Jet-lag and shift work: (2) therapeutic use of melatonin

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J R Soc Med 1999;**92**:402–405 SECTION OF OCCUPATIONAL MEDICINE, 29 OCTOBER 1998

The preceding article[1] has laid the foundations for understanding the difficulties of jet-lag and shiftworker's malaise and for appreciating the various countermeasures other than chronobiotics (drugs that alter rhythms).

Several approaches have met with some success. One of the major difficulties in this area is the uncontrollable nature of field studies on jet-lag and our inability to simulate time-zone change in the laboratory in a way that takes account of all the factors that may arise in the field.

COUNTERMEASURES

Studies in blind subjects and tolerant shift workers[2] indicate that at least some people are quite able to sleep out of phase without perceived ill-effects. Thus the initial strategy must be to ensure adequate sleep. Caffeine and alcohol have detrimental effects on sleep and should be avoided, though alcohol may promote sleep onset. Specifically timed naps before, during or after a flight or night-shift work can greatly increase alertness[3], and computer programs are available that predict alertness as a function of nap timing[4]. However, napping is often not possible. Passengers in first and business class will clearly have more opportunity than cabin-class passengers to sleep during a flight since the size and angle of the seats together with foot rests are more conducive to sleep. As far as possible, sleep should be taken during the future night-time in the destination time zone.

Hypnotics

Of the numerous studies on the effects of hypnotic drugs[3,5], some have suggested a speeding of circadian adaptation. The overriding factor when considering use of a hypnotic is the drug's duration of action: clearly the benefits associated with improved sleep may be masked if the hypnotic later causes unwanted drowsiness. After a transmeridian flight, hypnotics with a duration of action of around 3–5 hours may be useful to sustain sleep during the adaptation phase without adverse effects on performance. In these circumstances the benefits are likely to stem from their sleep promoting properties rather than a shift of circadian rhythm. As well as using hypnotic drugs on arrival in a new time zone, passengers may consider using them on the flight itself at bedtime in the destination time zone.

Melatonin

Melatonin can be thought of as a 'darkness' hormone. It is normally made at night and the duration of secretion reflects the length of the night. It seems to serve similar functions in all life forms so far studied—namely, to act as a time signal for the organization of daily and annual rhythms[6]. In animals that use day-length changes to time their seasonal cycles, melatonin indicates the length of the night. For example, a long night of melatonin in the autumn induces sheep to start breeding and hamsters (which breed in the summer) to stop breeding. Other seasonal variations such as coat growth are timed by melatonin. In some species, especially some lower vertebrates and birds, melatonin is essential for the organization of daily (circadian) rhythms. In mammals it is not essential for circadian organization but seems to reinforce behaviour associated with darkness—for example, sleep in man. It has rapid, transient, mild sleep-inducing effects and lowers alertness and body temperature during the 3–4 hours after a low dose (0.5–5 mg), these effects being opposite to the acute effects of bright light[6,7].

In the same dose range melatonin can either advance or retard the internal clock according to the timing[6–9]. As with light, the appropriate timing can be predicted from a phase response curve in subjects whose body clock phase is known. The phase response curve to melatonin is essentially the reverse of that to light[8,9]. Melatonin given about 8–13 hours before core temperature minimum will phase-advance and given about 1–5 hours after core temperature minimum will phase-delay.

In principle, if we could shift instantly and reliably the circadian clock by whatever means, all problems due to the endogenous clock would be countered. Thus a search has been initiated for a treatment which does just this. The effects of melatonin on the circadian system seem both more complex and much weaker than those of light. For example, it does not consistently entrain free-running circadian rhythms of core temperature[9]. In subjects synchronized to a normal 24-hour environment, timing of desired phase shifts is relatively simple and can to some extent be judged by their habitual sleep times. Optimal

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timing is not so simple after time-zone travel, in shift-workers and in blind subjects. Melatonin is available in the UK from a licensed manufacturer on prescription, but more freely in some other countries. Only licensed preparations have guaranteed content and purity.

SIMULATED PHASE SHIFTS

In environmental isolation, studies with advanced (eastward) phase shift and suitably timed melatonin treatment (5 mg) have shown an increase in the rate of re-entrainment of temperature, hormonal and electrolyte rhythms[10] but inconsistent effects on sleep. In one study with a simulated acute 9-hour delay of sleep time, the effectiveness of bright light (4 hours, 4–7000 lux) for three days during the first half of the night shift period, dim red light (50 lux) for the same period, melatonin and placebo taken just before and during desired sleep time were compared. Essentially only the bright light group showed significant circadian adaptation and improvements in performance, whereas both melatonin and bright light improved sleep[11].

After a simulated rapid 9-hour phase advance we investigated the ability of melatonin to hasten adaptation. Melatonin (5 mg fast release) or placebo was taken at 2300 h on the first night after the shift and for two further nights. Melatonin consistently improved sleep (quality, duration and night awakenings) compared with placebo and this action seemed independent of the direction of phase shift[12]. Daily mean alertness and performance efficiency were higher with melatonin than with placebo. Polysomnography indicated significant differences only on the first night after the shift, when total sleep time, sleep efficiency, and stage 1 and stage 2 sleep all increased but slow wave sleep decreased compared with placebo. There were no effects on rapid-eye-movement sleep[13].

The effects of melatonin were immediately evident, before phase adaptation had occurred. They seemed to be related to its acute effects on behaviour and temperature reinforced by a hastening of phase adaptation. The latter, however, is unlikely to play a major role at least during the first post-phase-shift days. It must be emphasized that simulations of this sort do not fully mimic real-life conditions—for example, sleep disorders continue for longer in field studies.

FIELD STUDIES ON JET-LAG

These are at least 9 placebo-controlled field studies[14–23] on the use of melatonin to alleviate perceived jet-lag (primarily sleep disturbance). Of these, 7 were successful in the sense that subjective (and in one case objective) measures of sleep and alertness improved versus placebo. The first study[14,15], over eight time zones eastwards, used a sequence of administration (5 mg melatonin daily) designed (a) to initiate an eastward phase shift before departure by early-evening administration (1800 h) for three days before the flight, and (b) to reinforce the advance by bedtime (2300 h) administration in the new time zone for four days. Both subjective and objective measures of jet-lag improved in the melatonin-treated group. In larger studies of travellers to Australia and New Zealand from the UK and back, a substantial improvement of subjective jet-lag was seen with melatonin (5 mg)[16,17]. After six, nine and eleven time zone changes, cortisol rhythms adapted more quickly and subjective jet-lag was consistently less, though not significantly so, both eastward and westward.

Pre-flight treatment at 2200 h and then daily for three days post-flight at bedtime (8 mg) led to improved sleep and less subjective jet-lag in 37 subjects travelling eastwards from the USA and Canada to France[19].

Comperatore *et al.*[20] used melatonin 10 mg daily combined with other countermeasures (timed avoidance of and exposure to bright light, pre-flight shift of bedtimes) to adapt to an 8-hour advance, but with unusual bedtimes (0400 h local time) at the destination. Melatonin treatment led to improved sleep duration and cognitive performance compared with the placebo group. Interestingly in view of the large dose of 10 mg, mild sleepiness and fatigue were reported only 'occasionally' after ingestion and never after awakening. This dose of melatonin will not be fully cleared from the circulation after 8 hours, but does not seem to cause 'hangover' (even Waldhauser, who used 80 mg, did not observe hangover effects).

In the largest controlled study reported to date, 320 individuals were treated at bedtime for four days after an eastward flight (6–8 time zones). Melatonin (5 mg fast release) was strikingly more efficient than placebo at improving sleep latency, sleep quality, daytime sleepiness and fatigue. A lower dose (0.5 mg) of a fast-release preparation was less effective, as was a slow-release preparation[21].

These positive reports contrast with two other studies. One[22] was in 52 aircrew travelling from Auckland to Los Angeles and returning to Auckland via London. The last leg was used for the trial. They reported problems with pre-flight melatonin administration (three days) and improvement in subjective measures with post-flight treatment only. In another large controlled study,[21] 249 subjects in four groups took 5 mg or 0.5 mg at bedtime and 0.5 mg on a shifting schedule to phase-advance the internal clock (New York to Oslo) but melatonin was completely ineffective at alleviating subjective symptoms of jet-lag. It should be noted that in all the successful previous studies the participants were either demonstrably or theoretically synchronized to the local environment before treatment. As with long-haul aircrew, the circadian state of the subjects was unknown before departure and four days was probably

not enough for full synchronization to New York time. The timing of melatonin seems critical, and the subjects may have received the treatment at an inappropriate circadian phase pre-flight. A method for rapid assessment of circadian phase would be highly desirable.

In both controlled and uncontrolled field studies on the travelling public over the past 10 years[7,24] we have observed an overall 50% reduction in subjectively assessed jet-lag symptoms (n=474) with 5 mg fast-release melatonin. Eastwards we currently use a single-phase advancing pre-flight early evening treatment followed by treatment at bedtime for four days after arrival. Westwards we advise taking melatonin for four days at bedtime (2300 h or later: a phase delay time over more than six time zones) in the new time zone. This timing allows exploitation of both sleep-inducing and phase-shifting effects. The subjective improvement increases with the number of time zones crossed. Short stopovers may require specific instructions.

Most of the published studies have proved positive. Nevertheless there is a need to explore the limitations of the treatment. We have little information on optimal dose or formulation. The pharmacokinetics of fast-release melatonin vary greatly between individuals and the question of individual sensitivity has not been addressed fully. There is no information on long-term safety, although to date no hazards in healthy adults have been reported. The treatment seems most successful in subjects synchronized to the local environment before departure and it is a matter for further experiment whether or not pre-flight administration confers any advantages. Since melatonin can specify the direction in which the clock adapts[10], it should probably be given before exposure to natural bright light or other time cues.

Avoidance of natural secretion of melatonin, by means of bright light or drugs, or in the future receptor antagonists, is an important consideration. There is already one report suggesting that suppression of melatonin with a beta-blocker facilitated phase shifts to bright light[25].

FIELD STUDIES ON SHIFT WORK

The use of melatonin to aid adaptation to a night shift has been reported in two field studies[26,27], both in 7-day-rotating shift workers. Melatonin at desired bedtime (early morning), designed to phase-delay, significantly improved day sleep duration and quality and night shift alertness. Its effects on performance tasks were variable. In one study melatonin improved the synchrony between endogenous circadian rhythms and daytime sleep. An important unanswered question is whether such facilitated adaptation by melatonin is accompanied by consistent changes in work related performance.

Avoidance of natural bright light may well be the most important consideration. There is good evidence that exposure to natural light when returning home in the early morning after a night shift opposes the delay required to sleep well during the day[28]. If one travels eastwards over more than four time zones and arrives in the early morning, light exposure will oppose adaptation. Strategies for light avoidance and treatment times have been proposed[29].

CONCLUSION

Melatonin and light may act in concert to maintain endogenous circadian synchronization. Avoidance of light is an important consideration since inappropriate light exposure can hinder adaptation. The combined use of melatonin and light should provide optimum phase-shifting strategies. For travellers I offer the following advice:

- Choose daytime flights to minimize loss of sleep and fatigue
- Travel business or first class
- Avoid large meals out of phase, avoid caffeine and alcohol during flight, drink lots of water
- Avoid taking critical decisions for the first day after arrival
- Avoid or seek bright light as appropriate
- Consider taking a short-acting hypnotic during the flight (so as to sleep during the destination night-time) and for the first few days after arrival
- Consider, with the advice of a physician, the use of melatonin if a licensed quality controlled preparation, with instructions for use, is available. Use the lowest effective dose. Be aware that there are very few short-term and no long-term safety data[30].

Acknowledgments My work is supported by the Ministry of Defence, the Wellcome Trust, the British Heart Foundation, the Medical Research Council, the European Commission, and Stockgrand Ltd. I am managing director of Stockgrand Ltd: this company supplies reagents and expertise for my experimental work.

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